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Steven F. Weinstock
Abbott Laboratories
Department 377 / AP6D-2
100 Abbott Park Road
Abbott Park, IL 60064-6050

EXAMINER
MOORE, WILLIAM W

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1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/735,056	Applicant(s) KATZ ET AL.	
	Examiner William W. Moore	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-83* is/are pending in the application.

4a) Of the above claim(s) *63-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-62 and 72-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *57-83* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary Amendments

Applicant's Preliminary Amendment A, Paper No. 8 filed with the application on December 11, 2000, has been entered, canceling the original claims 1-56 in favor of entry of the new claims 57-83 and providing an incorporation by reference at page 1, line 1, of the instant specification of the disclosures of the various priority documents within the instant specification.

Information Disclosure Statement

Applicant's Information Disclosure Statement, Paper No 4 filed March 22, 2001, has been entered and considered, save for the publications of Li et al., Motamedi et al. and Robinson, listed as references C38, C43 and C49 on Applicant's PTO Form 1449, which are undated and for which no dates can be determined on the basis of the texts of the references. Thus entries for each of references C38, C43 and C49 are lined-through and are not initialed on Applicant's PTO Form 1449, and the references were not considered.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. §121:

I. Claims 59 and 60 drawn specifically to, and claims 57, 58 and 72-83 drawn in part to, a method for directing biosynthesis of polyketide analogs comprising the recombinant inactivation of encoded domains providing polyketide ß-carbonyl processing functions, classified in class 435, subclass 471.

II. Claims 61 and 62 drawn specifically to, and claims 57, 58 and 72-83 drawn in part to, a method for directing biosynthesis of polyketide analogs comprising the recombinant addition of encoded domains providing polyketide ß-carbonyl processing functions, classified in class 435, subclass 471.

III. Claims 63 and 64 drawn specifically to, and claims 57, 58 and 72-83 drawn generically to, a method for directing the biosynthesis of polyketide analogs comprising the recombinant inactivation of encoded domains providing polyketide carbon unit condensation functions, classified in class 435, subclass 471.

IV. Claims 66 and 67 drawn specifically to, and claims 57, 58, 65 and 72-83 drawn in part to, a method for directing the biosynthesis of polyketide analogs comprising the recombinant addition of encoded domains providing polyketide elongation or enlargement, classified in class 435, subclass 471.

V. Claims 68-70 drawn specifically to, and claims 57, 58, 65 and 72-83 drawn in part to, a method for directing the biosynthesis of polyketide analogs comprising the recombinant deletion of encoded domains providing polyketide shortening or diminution, classified in class 435, subclass 471.

VI. Claim 71, drawn specifically to, and claims 57, 58 and 72-83 drawn in part to, a method for directing the biosynthesis of polyketide analogs comprising the recombinant substitution of encoded domains providing polyketide acyltransferase functions, classified in class 435, subclass 471.

Inventions of Group I and Groups II-VI are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, the invention of Group I has separate utility such as directing the biosynthesis of polyketide analogs having an increase in unprocessed ß-carbonyl units while the inventions of Groups II-VI need not. See MPEP § 806.05(d).

Inventions of Group II and Groups III-VI are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, the invention of Group II has separate utility such as directing the biosynthesis of polyketide analogs having an increase in processed ß-carbonyl units while the inventions of Groups I and III-VI need not. See MPEP § 806.05(d).

Inventions of Group III and Groups IV-VI are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, the invention of Group III has separate utility such as directing the biosynthesis of polyketide analogs having an absence of specific ketide units while the inventions of Groups I, II and VI-VI need not. See MPEP § 806.05(d).

Inventions of Group IV and Groups V and VI are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, the invention of Group IV has separate utility such as directing the biosynthesis of extended polyketide analogs while the inventions of Groups I-III, V and VI need not. See MPEP § 806.05(d).

Inventions of Group V and Group VI are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, the invention of Group V

has separate utility such as directing the biosynthesis of truncated polyketide analogs while the inventions of Groups I-IV and VI need not. See MPEP § 806.05(d).

Because these inventions are distinct for the reasons given above and the search required for any one of Groups I-VI is not required for another among Groups I-VI, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Diane Casuto on August 30, 2002, a provisional election was made with traverse to prosecute the invention of Group I, claims 59 and 60 specifically, and claims 57, 58 and 72-83 in part. In view of the common disclosure in a priority document of the addition and inactivation of polyketide ß-carbonyl processing function, the restriction requirement above is RESCINDED as between Groups I and II and claims 61 and 62 are also examined herein. Affirmation of this election must be made by applicant in replying to this Office action. Claims 63-71 are withdrawn in whole and claims 57, 58 and 72-83 are examined to the extent they describe a method requiring an addition or inactivation of a polyketide ß-carbonyl processing function and are withdrawn in part from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention to the extent they do not describe a method requiring an addition or inactivation of a polyketide ß-carbonyl processing function.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claims 57, 73, 77 and 83 are objected to because of the following informalities: The word "containing" in clause (3) of claim 57 is misspelled and the word "consisting" is misspelled at line 2 of claim 73 and at line 2 of claim 77. Claim 83 refers back to the canceled claim 23 rather than to a pending claim. Appropriate correction is required.

Objection to the Specification

The specification is objected to and a substitute specification is REQUIRED in response to this communication because the instant specification contains not a single word that supports the subject matter of the elected claims and the public reading the present specification and claims, should claims to Applicant's elected invention be allowed, would

have no idea what might be used to practice the methods of the elected claims. The substitute specification must include descriptions in application serial No. 07/642,734 - the priority document which is now U.S. Patent No. 5,824,513 - of the preparation of products with which practice of the elected methods for biosynthesis of specific polyketides requiring alteration of a DNA sequence that encodes a polyketide synthase [PKS], wherein BKS ß-ketoreductase, dehydratase, and/or enoylreductase domains domain are inactivated and/or added, is possible. Specifically, claims 57-62 and 72-83 must be supported by including the disclosures of U.S. Patent No. 5,824,513, of Figure 3, Examples 1-16 at cols. 8-13, Examples 27-44 at cols. 16-21, and at least as much of col. 4 therein as comprises lines 63-66, although more of col. 4 may be also be included. The instant specification must be amended by such textual incorporation from the specification of the priority document pursuant to 37 CFR 1.125(a).

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original priority document, the original specification, and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-62, 72-75, 77, 78, 82 and 83 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is agreed that the specification of the initial priority document, application serial No. 07/642,734 - now U.S. Patent No. 5,824,513 - describes the preparation of products with which methods of claims 57-60, 72-75, 77, 78, 82 and 83 for the biosynthesis of specific erythromycin analogs might be practiced by alteration of a DNA sequence that encodes a polyketide synthase [PKS] so that two *Saccharopolyspora erythraea eryA* ß-ketoreductase domains and a *Saccharopolyspora erythraea eryA* dehydratase domain are inactivated. While the priority document neither exemplifies nor describes the preparation of products with which to practice methods of claims 57-60, 72-75, 77, 78, 82 and 83 which are methods for directing biosynthesis of specific polyketides requiring alteration of a PKS-encoding DNA sequence by inactivating one or more enoylreductase domains, the priority document suggests this be done, see col. 4 at lines 63-66, and teaches the identification of a *Saccharopolyspora erythraea eryA* enoylreductase domain. The priority document also describes preparation of products with which to practice methods of claims 57-60, 72-75, 77, 78, 82 and 83 for directing biosynthesis of specific erythromycin analogs requiring alteration of a DNA sequence encoding a polyketide synthase [PKS] so that each of a *Saccharopolyspora erythraea eryA* ß-ketoreductase, *eryA* dehydratase, and *eryA* enoylreductase domain is added. While these domain additions may be characterized as replacements because they comprise further domains of a *Saccharopolyspora erythraea* PKS module in a substitution of a disabled module, they meet the statutory requirement for an adequate written description because a DNA sequence comprising regions specifying the required *Saccharopolyspora erythraea eryA* domains are sequestered, placed in a plasmid, and then transferred to a location in the *Saccharopolyspora erythraea eryA* gene in which nucleic acid sequences encoding the transferred domains did not previously reside.

The instant specification fails to describe the design and preparation of PKS proteins wherein ß-ketoreductase, dehydratase, or enoylreductase domains other than those of the

Saccharopolyspora erythraea eryA-encoded PKS are either inactivated or added in an altered PKS product by mutation of the underlying PKS gene. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Even if disclosures of the priority document are textually incorporated, the instant specification nowhere furnishes relevant identifying characteristics of any altered PKS but a *Saccharopolyspora erythraea eryA*-encoded PKS with which generic methods of claims 57-60, 72-75, 77, 78, 82 and 83 might be practiced. Applicant provides no disclosure, or any specific suggestion, of an adequate number of diverse, heterogeneous, domain species to establish an adequate written description of a generic PKS product for the practice of methods of the elected claims wherein a PKS is modified by inactivation or addition of generic PKS ß-ketoreductase, dehydratase, or enoylreductase domains.

The Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Nothing in the present specification demonstrates that Applicant was "able to envision" enough of the structure of altered, generic, PKS products to provide the public with identifying "characteristics [that] sufficiently distinguish [them] . . . from other materials" with which to practice methods of the elected claims. *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed, generic, subject matter is considered to be entirely prospective where skilled artisans in the relevant field of

molecular biology could not predict the structure, or other properties, of the generic PKS products required for practice of the claimed generic methods.

Claims 59-62, 72-75, 77, 78, 82 and 83 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for methods of directing the biosynthesis of specific erythromycin analogs wherein a specific, modified, PKS comprising the inactivation or addition of one or more of the *Saccharopolyspora erythraea eryA*-encoded ß-ketoreductase, dehydratase, or enoylreductase domains is designed and an actinomycete host cell is transformed with the nucleic acid sequence encoding the specific, modified, PKS and grown in culture conditions,

does not reasonably provide enablement for any method of directing the biosynthesis of generic macrolides, tetracyclines, polyethers, polyenes, ansamycins, or any analogs or derivatives thereof, utilizing a modified, PKS comprising the addition of one or more generic ß-ketoreductase, dehydratase, or enoylreductase domains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While claim 57 recites "specific macrolide polyketide analogs", and claim 77 sweeps more broadly in reciting, "macrolides, tetracyclines, polyethers, polyenes, ansamycins, and analogs or derivatives thereof", Applicant's priority document discloses only methods of the elected claims 59-62 permitting the preparation of specific erythromycin analogs. Thus claims 59-62, 72-75, 77, 78, 82 and 83 herein contemplate arbitrary assignments of any or all of PKS ß-ketoreductase, dehydratase, or enoylreductase domain inactivations or additions in a generic PKS in order to practice a method for directing the biosynthesis of, at least, generic macrolides, and, according to claim 77, a lot more. It is agreed that, based on disclosures of Applicant's priority document, Applicant enables methods for directing the biosynthesis of generic macrolide analogs and derivatives wherein a generic PKS capable of conducting macrolide biosynthesis is altered by inactivation of one or more of its native PKS ß-ketoreductase, dehydratase, or enoylreductase domains. This rejection is stated under the first paragraph of the statute because neither the instant specification nor the specification of the priority document can support the addition of heterologous PKS ß-ketoreductase, dehydratase, or enoylreductase domains to native domains present in the PKS encoded by the *Saccharopolyspora erythraea eryA* gene in a method for directing

the biosynthesis of erythromycin analogs, or analogs of other macrolides, nor the addition of *S. erythraea eryA*-encoded ß-ketoreductase, dehydratase, or enoylreductase domains in a heterologous PKS in a method for directing the biosynthesis of erythromycin analogs, or analogs of other macrolides. Mere perturbation or dispersal of heterologous, undisclosed, ß-ketoreductase, dehydratase, or enoylreductase domains cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent PKS products and provide the public with method for directing the biosynthesis of other macrolide or methods for directing the biosynthesis of any tetracyclines, polyethers, polyenes, ansamycins, and analogs of derivatives thereof.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a

single B-cell growth factor allele). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

The Federal Circuit has also considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence to embrace a specific variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands*, ***supra***, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for adding undisclosed DNA sequences coding for, and encoded amino acid sequences of, ß-ketoreductase, dehydratase, or enoylreductase domains to any among the numerous members of genera of macrolide-, tetracycline-, polyether-, polyene-, and ansamycin-biosynthetic molecules, to the extent recited in the claims,

b) the specification lacks working examples wherein any but *S. erythraea eryA*-encoded ß-ketoreductase, dehydratase, or enoylreductase domains, are added to the modular array of domains in any other PKS,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no other members of the genus of macrolide biosynthetic PKS molecules, or analogs of derivatives thereof, nor any members at all of the genera of PKS molecules responsible for the biosynthesis of tetracyclines, polyethers, polyenes, ansamycins, not analogs of derivatives thereof, have had regions specifically identified for modification by addition(s) of generic ß-ketoreductase, dehydratase, or enoylreductase domains, or the *S. erythraea eryA*-encoded ß-ketoreductase, dehydratase, or enoylreductase domains disclosed in the priority document.

The scope of claimed subject matters embraced by generic methods for directing the biosynthesis of generic macrolides, tetracyclines, polyethers, polyenes, ansamycins, and analogs of derivatives thereof, requiring either the addition of generic ß-ketoreductase, dehydratase, or enoylreductase domains or the addition of *Saccharopolyspora erythraea eryA*-encoded ß-ketoreductase, dehydratase, or enoylreductase domains to heterologous,

generic, macrolide-, tetracycline-, polyether-, polyene-, and ansamycin-biosynthetic PKS molecules, is unsupported by the present specification, even if taken in combination with the teachings available in the prior art. In order to overcome this rejection, Applicant is invited to present evidence demonstrating that addition of, at least, the *Saccharopolyspora erythraea eryA*-encoded ß-ketoreductase, dehydratase, and/or enoylreductase domains to heterologous macrolide-, tetracycline-, polyether-, polyene-, and ansamycin-biosynthetic PKS molecules, and analogs of derivatives thereof, can permit artisans to direct biosynthesis of specific macrolides, tetracyclines, polyethers, polyenes, ansamycins, and their analogs or derivatives.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-62 and 72- 83 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 is indefinite in reciting, "enzymatic activities associated within", in clause (2) because DNA sequences have no "enzymatic" activity "within"; instead, DNA sustains its biological functions of retaining and transmitting information by virtue of its biochemical inactivity. Applicant had intended to describe, e.g., a DNA sequence region encoding a PKS domain having an enzymatic activity. Claim 57 is again indefinite in reciting, "DNA sequence which codes for one of said enzymatic activities" in clause (3) and in similarly reciting, in clause (5), "which encode the enzymatic activities comprising", because nucleic acid sequences do not encode "activities" but instead encode polypeptide products that have enzymatic activities. Applicant intended to indicate that a DNA sequence encodes a **domain having an enzymatic activity** within a very large polyprotein, a polyketide synthase such as that encoded by, e.g., the *eryA* gene. Clause (4) of claim 57 is further indefinite in reciting "the original sequence" where the claim has no antecedent basis for the term

"original" elsewhere. Claims 81 and 82 are similarly rejected as indefinite because claim 81 recites, "DNA sequence . . . encodes the enzymatic activities associated with", and claim 82 recites, "DNA sequence encodes one or more enzymatic activities". The remaining elected claims 58-62, 72-80 and 83 are included in this rejection because they fail to correct the indefinite description of claims 57 and 82 from which they depend.

Claim 77 is independently indefinite in its dependency from claim 57, where claim 57 describes methods "for directing the biosynthesis of specific macrolide polyketide analogs" but claim 77 confusingly indicates that tetracyclines, polyethers, polyenes, ansamycins and "derivatives or analogs thereof" are among the desired, "specific macrolide [ ] analogs", to be produced, or perhaps are precursors for the biosynthesis that might be converted to "specific macrolide [ ] analogs". Claim 78 is rejected together with claim 77 because it states that "said polyketide is a macrolide", thus its subject matter does not clearly differ in scope from that of claim 57 from which it ultimately depends. Claim 83 is rejected as indefinite because the nature of the method Applicant intended that it further limit cannot be determined.

Allowable Subject Matter

To the extent that claims 57-62 and 72-83 describe Applicant's elected methods of directing the biosynthesis of specific polyketide analogs requiring the alteration of a PKS-encoding DNA sequence to produce a specific, modified, PKS wherein either one or more ß-ketoreductase, dehydratase, or enoylreductase domains of the PKS are inactivated or one or more PKS ß-ketoreductase, dehydratase, or enoylreductase domains have been added to the native PKS, they are free of the prior art of record which must have a publication date, or an earlier effective filing date in the case of a published U.S. Patent, before Applicant's initial disclosure of such modifications of a native PKS in the January 1991-filed priority application. Weber et al., October 1985, made of record with Applicant's

Information Disclosure Statement, did not practice a method that comprised steps (4)-(6) of claim 57. While each of Weber et al., May 1990, Tuan et al., April 1990, and Richardson et al., also made of record with Applicant's Information Disclosure Statement, practiced steps (1) through (5) of claim 57, each fails to disclose any *S. erythraea eryA*I mutant, or *S. ambofaciens srm*G mutant, producing erythromycin or spiramycin analogs evidencing a failure in activity of a PKS ß-ketoreductase, dehydratase, or enoylreductase domain, thus do not clearly establish an inherent disclosure of a claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 7:00AM-5:30PM EST on Mondays and Wednesdays, between 7:00AM-1:30PM EST on Tuesdays and Thursdays, and between 8:30AM and 5:00PM EST on Fridays. **The examiner's direct FAX telephone number is 703.746.3169.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
September 24, 2002

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600